PAFAH1B1 gene

platelet activating factor acetylhydrolase 1b regulatory subunit 1

Normal Function

The *PAFAH1B1* gene (also known as *LIS1*) provides instructions for making a protein that is one part (subunit) of a complex called platelet activating factor acetyl hydrolase 1B (PAFAH1B). In the brain, this complex regulates the level of a molecule called platelet activating factor (PAF). PAF is thought to be involved in directing the movement of nerve cells in the brain, a process known as neuronal migration. Proper neuronal migration is essential for normal brain development and function.

Separate from its role in the PAFAH1B complex, the PAFAH1B1 protein is also likely involved in the organization of the cell's structural framework (the cytoskeleton). This protein interacts with microtubules and regulates a variety of proteins that are involved in their function. Microtubules are rigid, hollow fibers that make up the cytoskeleton, and they are involved in cell division and movement.

Health Conditions Related to Genetic Changes

isolated lissencephaly sequence

More than 70 mutations in the *PAFAH1B1* gene have been found to cause isolated lissencephaly sequence (ILS). This condition is characterized by abnormal brain development that results in the brain having a smooth appearance (lissencephaly) instead of its normal folds and grooves. Individuals with ILS have severe neurological problems, including intellectual disability and recurrent seizures (epilepsy). Most of the *PAFAH1B1* gene mutations that cause ILS lead to the production of an abnormally small, nonfunctional version of the PAFAH1B1 protein. *PAFAH1B1* gene mutations account for over half of all ILS cases.

As a result of *PAFAH1B1* gene mutations, PAF levels are uncontrolled and the normal function of microtubules is impaired. Neurons in the developing brain are particularly affected, which impairs brain development and leads to the severe neurological problems characteristic of ILS.

Miller-Dieker syndrome

The characteristic signs and symptoms of Miller-Dieker syndrome are caused by a deletion of genetic material near the end of the short (p) arm of chromosome 17. The chromosomal region that is typically deleted contains multiple genes, including the *PAFAH1B1* gene. As a result of the deletion, people with this condition have only one copy of the *PAFAH1B1* gene in each cell instead of the usual two copies.

A deletion of one copy of the *PAFAH1B1* gene in each cell reduces the amount of PAFAH1B1 protein by about half. Researchers believe that a shortage of this protein is responsible for many of the features of Miller-Dieker syndrome, including intellectual disability, developmental delay, and epilepsy. A decrease in neuronal migration caused by a lack of PAFAH1B1 protein is responsible for the lissencephaly that is characteristic of Miller-Dieker syndrome.

Other genes deleted in the same region of chromosome 17 are responsible for the other features of Miller-Dieker syndrome such as distinctive facial features, slow growth, and breathing difficulties.

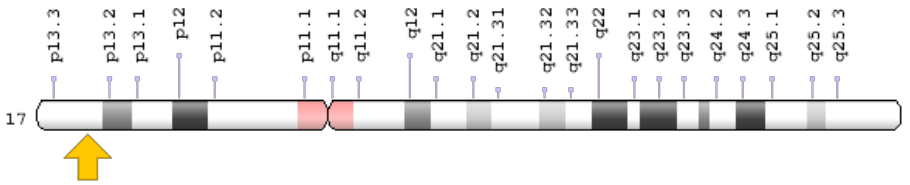
other disorders

In some cases, *PAFAH1B1* gene mutations are present in only some of the body's cells, a situation known as mosaicism. Mosaicism for *PAFAH1B1* gene mutations causes a less severe brain abnormality called subcortical band heterotopia. This abnormality occurs when neurons migrate to an area of the brain where they are not supposed to be (heterotopia) and form abnormal band-like clusters. Since these bands are located beneath the cerebral cortex, they are said to be subcortical. The signs and symptoms of subcortical band heterotopia vary from severe intellectual disability and epilepsy to normal intelligence with mild or no epilepsy.

Chromosomal Location

Cytogenetic Location: 17p13.3, which is the short (p) arm of chromosome 17 at position 13.3

Molecular Location: base pairs 2,593,210 to 2,685,617 on chromosome 17 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- LIS1
- LIS1_HUMAN
- LIS2

- lissencephaly 1 protein
- MDCR
- platelet-activating factor acetylhydrolase 1b, regulatory subunit 1 (45kDa)
- platelet-activating factor acetylhydrolase, isoform Ib, alpha subunit
- platelet-activating factor acetylhydrolase, isoform Ib, subunit 1 (45kDa)

Additional Information & Resources

Educational Resources

- Neuroscience (second edition, 2001): Neuronal Migration
  https://www.ncbi.nlm.nih.gov/books/NBK10831/

GeneReviews

- LIS1-Associated Lissencephaly/Subcortical Band Heterotopia
  https://www.ncbi.nlm.nih.gov/books/NBK5189

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28PAFAH1B1%5BTIAB%5D%29+OR+%28LIS1%5BTI%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D

OMIM

- PLATELET-ACTIVATING FACTOR ACETYLHYDROLASE, ISOFORM 1B, ALPHA SUBUNIT
  http://omim.org/entry/601545

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_PAFAH1B1.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=PAFAH1B1%5Bgene%5D
- HGNC Gene Family: WD repeat domain containing
  http://www.genenames.org/cgi-bin/genefamilies/set/362
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=8574

- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/5048
- UniProt
  http://www.uniprot.org/uniprot/P43034

Sources for This Summary

- Cardoso C, Leventer RJ, Dowling JJ, Ward HL, Chung J, Petras KS, Roseberry JA, Weiss AM, Das S, Martin CL, Pilz DT, Dobyns WB, Ledbetter DH. Clinical and molecular basis of classical lissencephaly: Mutations in the LIS1 gene (PAFAH1B1). Hum Mutat. 2002 Jan;19(1):4-15. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11754098
- Cardoso C, Leventer RJ, Ward HL, Toyo-Oka K, Chung J, Gross A, Martin CL, Allanson J, Pilz DT, Olney AH, Mutchinick OM, Hirotsune S, Wynshaw-Boris A, Dobyns WB, Ledbetter DH. Refinement of a 400-kb critical region allows genotypic differentiation between isolated lissencephaly, Miller-Dieker syndrome, and other phenotypes secondary to deletions of 17p13.3. Am J Hum Genet. 2003 Apr;72(4):918-30. Epub 2003 Mar 5.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12621583
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1180354/
- Friocourt G, Marcorelles P, Saugier-Veber P, Quille ML, Marret S, Laquerrière A. Role of cytoskeletal abnormalities in the neuropathology and pathophysiology of type I lissencephaly. Acta Neuropathol. 2011 Feb;121(2):149-70. doi: 10.1007/s00401-010-0768-9. Epub 2010 Nov 3. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21046408
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3037170/
- Liu JS. Molecular genetics of neuronal migration disorders. Curr Neurol Neurosci Rep. 2011 Apr; 11(2):171-8. doi: 10.1007/s11910-010-0176-5. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21222180
- OMIM: PLATELET-ACTIVATING FACTOR ACETYLHYDROLASE, ISOFORM 1B, ALPHA SUBUNIT
  http://omim.org/entry/601545
- Pilz DT, Kuc J, Matsumoto N, Bodurtha J, Bernadi B, Tassinari CA, Dobyns WB, Ledbetter DH. Subcortical band heterotopia in rare affected males can be caused by missense mutations in DCX (XLIS) or LIS1. Hum Mol Genet. 1999 Sep;8(9):1757-60.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/10441340
- Reiner O, Carrozzo R, Shen Y, Wehnert M, Faustinella F, Dobyns WB, Caskey CT, Ledbetter DH. Isolation of a Miller-Dieker lissencephaly gene containing G protein beta-subunit-like repeats. Nature. 1993 Aug 19;364(6439):717-21.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/8355785
- Saillour Y, Carion N, Quelin C, Leger PL, Boddaert N, Elie C, Toutain A, Mercier S, Barthez MA, Milh M, Joriot S, des Portes V, Philip N, Broglin D, Roubertie A, Pitelet G, Moutard ML, Pinard JM, Cances C, Kaminska A, Chelly J, Beldjord C, Bahi-Buisson N. LIS1-related isolated lissencephaly: spectrum of mutations and relationships with malformation severity. Arch Neurol. 2009 Aug;66(8): 1007-15. doi: 10.1001/archneurol.2009.149.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19667223

- Spalice A, Parisi P, Nicita F, Pizzardi G, Del Balzo F, Iannetti P. Neuronal migration disorders: clinical, neuroradiologic and genetics aspects. Acta Paediatr. 2009 Mar;98(3):421-33. doi: 10.1111/j.1651-2227.2008.01160.x. Epub 2008 Dec 16. Review.
Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19120042
- Sweeney KJ, Clark GD, Prokscha A, Dobyns WB, Eichele G. Lissencephaly associated mutations suggest a requirement for the PAFAH1B heterotrimeric complex in brain development. Mech Dev. 2000 Apr;92(2):263-71.
Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/10727864
- Wynshaw-Boris A. Lissencephaly and LIS1: insights into the molecular mechanisms of neuronal migration and development. Clin Genet. 2007 Oct;72(4):296-304. Review.
Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17850624

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